## REMARKS/ ARGUMENTS

Applicants note with appreciation the detail and thoroughness embodied in Paper No. 20070410 and the opportunity to distinguish the pending claims over the prior art of record. This amendment is submitted to be fully responsive thereto. Claims 8-16, 19, 20, 22, 24, 26, 27, and 30 are currently pending in this application.

Currently the Specification is objected to under 35 U.S.C. 132(a) as introducing new matter into the disclosure.

Currently, claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012). Claims 11, 15, and 16 stand rejected under 36 U.S.C § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197), and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and in further view of Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002). Claims 11, 12, 15, and 16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197), and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and in further view of Kitadai et al (Brit. J. Cancer 81(14): 647-653, 1999).

**Remarks Directed to the Objection of the Specification Under 35 U.S.C. 132(a): New Matter**

Withdrawal of the objections to the specification under 35 U.S.C. 132(a) is requested for at least the following reasons. The paragraph beginning at line 15 of page 9 in the subject application is currently amended to recite "cholic acid" in line 4 of page 10 as originally filed.

For at least the above reasons, applicants respectfully request all objections to the specification under 35 U.S.C. 132(a) be withdrawn.

**Remarks Directed to the Rejection of Claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012):**

Withdrawal of the rejection of claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) is respectfully requested for at least the following reasons. Niedzinski et al in view of Keener et al and Gebeyehu et al does not teach or suggest all limitations of the claimed invention.

Independent claims 8 and 20 are limited to "the group consisting of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, desoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, and taurochenodeoxycholic acid." Each and every element of claims 8 and 20 is not taught or suggested by Niedzinski in view of Keener and in view of Gebeyehu expressly or inherently. "To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Niedzinski teaches away from the use of bile acids that are not "C(3)-functionalized." Niedzinski teaches that "C(3)-functionalized cholic acid derivatives . . . interact with molecular receptors in the ileum, aiding delivery of molecules through the intestinal wall." (p. 722, first column.) Thus, Niedzinski teaches that functional delivery of DNA requires a C(3)-functionalized cholic acid derivative. The cholesterol derivatives of the instant claims are not C(3)-functionalized and are, thus, neither taught nor suggested by Niedzinski. Further, Niedzinski teaches that survival of the DNA in stomach or ileum fluid extracts depends on a complex of cholate amphiphiles with DOTAP and DOPE, not without these supporting synthetic lipids. (p. 725, first paragraph.) All further examples in Niedzinski depend on the presence of these supporting lipids for function of the cholic acid derivative. (Figs. 3-5.) Thus, Niedzinski teaches away from the independent use of a cholesterol derivative selected from the group consisting of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, desoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, and taurochenodeoxycholic acid."

Niedzinski teaches that "the robust nature of the C(3)-*N*-acyl imidazole should make this synthetic strategy adaptable to the synthesis of a variety of C(3) bile acid conjugates." Niedzinski is limited to teaching that a synthetic intermediate is suitable for the chemical synthesis of many unique derivatives of C(3)-functionalized cholic acid. Teaching the suitability of a chemical intermediate for multiple products is not akin to suggesting the suitability of those products for a different purpose. Niedzinski does not teach or suggest that the cholesterol conjugates of instant claims 8 and 20 are suitable for use as a stand alone delivery agent. Thus, Niedzinski does not teach or suggest any use of the cholesterol derivatives of the instant claims.

The teaching of Keener further fails to suggest the instant invention as the cholesterol derivatives of Keener are not functional equivalents of the C(3)-functionalized cholic acid

derivatives of Niedzinski nor of the compounds of the instant claims. The bile acids of Keener are not known material based on suitability for intended use as the Niedzinski teaches that suitability for delivery of DNA to cells requires both a C(3)-functionalized group and co-administration with synthetic lipids. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. MPEP 2144.06; *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). As the compounds of Keener are not equivalents of Niedzinski, the combination of Niedzinski and Keener does not teach or suggest the use of non-C(3)-functionalized cholesterol derivatives alone as suitable for delivery of DNA to cells as is claimed in the instant invention. Therefore, Niedzinski in view of Keener does not teach or suggest each and every limitation of the instant claimed invention.

Niedzinski in view of Keener in further view of Gebeyehu also fails to teach or suggest all elements of the instant invention. The "R" group of Gebeyehu et al. is taught only to be a C1-23 alkyl or alkenyl, or a steroid selected from the group consisting of stigmasterol, ergosterol and cholic acid. (col. 3, lines 61-64.) Gebeyehu provides no teaching or suggestion to use any cholesterol derivative other than stigmasterol, ergosterol, and cholic acid. Thus, Niedzinski in view of Keener and Gebeyehu does not teach or suggest the use of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, desoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, and taurochenodeoxycholic acid conjugated to a polyionic peptide by linker chemistry involving sulfur, nitrogen, or oxygen.

Furthermore, as Gebeyehu does not teach or suggest the subject inventive compositions of independent claim 8, the reference also does not teach or suggest a commercial package

comprising A-$R_1$-Q-Z as an active ingredient together with instruction for the use thereof as a nucleic acid delivery agent to a subject as in dependent claim 30.

As such, Niedzinski in view of Keener and Gebehehu does not teach or suggest each element of the instant claims. "To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. MPEP 2144.06; *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). One of ordinary skill in the art would not consider the prior art reference combination since Niedzinski et al teaches away from the use of non-C(3)-functionalized cholesterol derivatives. As such the prime facie case of obvious is respectfully submitted to have been rebutted.

In light of the above remarks, applicants respectfully request that the rejection of claims 8 and 30 under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) be withdrawn.

**Remarks Directed to the Rejection of Claims 11, 15, and 16 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Niedzinski et al (Lipids 35(7): 721-727, 2000), in View of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) in Further View of Perrie et al (J. Liposome Res. 12(1&2):185-197, 2002):**

Withdrawal of the Rejection of Claims 11, 15, and 16 Under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012), in further view of Perrie et al (J.

Liposome Res, 12(1&2):185-197, 2002) is respectfully requested for at least the following reasons. Niedzinski et al in view of Keener et al and Gebeyehu et al, in further view of Perrie et al does not teach or suggest all of the claimed limitations either expressly or inherently. "To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Perrie teaches oral delivery of a hepatitis B surface antigen (HbsAg) to mice such that the antigen is expressed on the surface of murine cells generating an immune response. Examiner correctly states that that HbsAg is a surface protein, and its surface expression requires expression and routing through a secretory pathway. However, HbsAg function as an antigenic compound is limited to exposure of the extracellular portion of the antigen as it remains integrally associated with the cell membrane. The antigen is not secreted but is merely expressed on the surface of a cell. Secreted proteins, in contrast, are not retained on the surface of an expressing cell, but are instead released via the secretory pathway into the extracellular milieu. The term secrete is defined by Stedman's Medical Dictionary "[t]o generate and separate a substance from cells or bodily fluids." (2nd edition, Houghton-Mifflin Co., 2004.)

Kitadai (Brit J Cancer 81(14): 647-653, 1999) teaches interleukin-8 to be a protein that is transfected and subsequently secreted by the transfected cells. (Table 2. secretion and release of interleukin-8 into cell culture supernatants stimulated HUVEC growth.) Thus, secreted as used in the art and in claims 11, 15 and 16 is neither taught nor suggested by Perrie's use of a cell surface retained HbsAg to produce immunogenicity.

Perrie et al. is limited to teaching oral administration of a liposome entrapped plasmid DNA molecule. This route of administration is distinct from the subject application. Perrie teaches that DNA by entrapment into liposomes is essential to its protection. (p. 186,

Introduction; p. 190.) Niedzinski supports Perrie by teaching function of cholate amphiphiles in the presence of liposomes only, and as such contraindicates the proposed prior art reference combination.

Applicants incorporate the arguments above that Niedzinski in view of Keener and Gebehehu both teaches away from the instant invention of independent claim 8 and does not teach each and every limitation of independent claim 8. For similar reasoning claims 15 and 16 are similarly nonobvious. Applicants reserve the right to make this reasoning express in due course. Therefore, Niedzinski in view of Keener and Gebehehu, in further view of Pierre does not teach or suggest each and every limitation of claims 11, 15, and 16.

In light of the above remarks, applicants respectfully request that the rejection of claims 11, 15, and 16 under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012), in further view of Perrie et al (J Liposome Res, 12(1&2):185-197, 2002) be withdrawn.

**Remarks Directed to the Rejection of Claims 11, 12, 15, and 16 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Niedzinski et al (Lipids 35(7): 721-727, 2000), in View of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) in Further View of Kitadai et al (Br J Cancer 81(14): 647-653, 1999):**

Withdrawal of the Rejection of Claims 11, 12, 15, and 16 Under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012), in further view of Kitadai et al (Br J Cancer 81(14): 647-653, 1999) is respectfully requested for at least the following reasons. Niedzinski et al in view of Keener et al and Gebeyehu et al, in further view of Kitadai et al does

not teach or suggest all of the claimed limitations either expressly or inherently. "To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Niedzinski teaches away from the use of a cholesterol derivative selected from the group consisting of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, desoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, and taurochenodeoxycholic acid to transfect cells as the function of the cholate amphiphiles of Niedzinski is taught to be dependent on C(3)-functionalization. (para. bridging pg. 721-22.) As such, there is no motivation in the art to combine the teaching of Niedzinski with Keener and Gebeyehu in the instant invention. Additionally as described above, combinations of elements in Niedzinski, Keener, and Gebeyehu et al. fail to yield the subject claimed invention.

Kitadai teaches transfection of human carcinoma cells with an expression vector housed in LIPOFECTIN vesicles. Niedzinski teaches that supplementing DOTAP/DOPE vesicles with cholate amphiphiles (5 and 6) does not interfere with the gastroprotection and that they may assist in transfection mediated by DOTAP/DOPE (p. 725-26), not that the cholate amphphiles can serve as functional substitutes for DOTAP/DOPE vesicles. There exists no motivation from the teaching of Niedzinski in view of Keener and Gebeyehu for a person having ordinary skill in the art to make this substitution. The teaching of Kitadai fails to correct this shortcoming, because Kitadai merely transfects cells with LIPOFECTIN encapsulated DNA. As the present inventive compounds are not equivalents to Niedzinski (see above), there exists no motivation to substitute the present inventive compounds for the cholate amphiphiles of Niedzinski into the method of Kitadai in place of LIPOFECTIN. Thus, a person having ordinary skill in the art

would not substitute the Niedzinski compound or the present inventive compounds for LIPOFECTIN reagent for use in the method of Kitadai.

Further, the *in vivo* delivery method of Kitadai is fully distinct from the instant inventive use. The instant claims are directed to targeting the cells of a "subject." Kitadai, in contrast, pre-transfects cells by the LIPOFECTIN method then delivers those cells to the cells of a subject. Thus, the teaching of Kitadai provides no motivation for a person having ordinary skill in the art to deliver naked conjugating agent-nucleic acid complex to a subject without prior transfection of cells.

As the subject inventive compounds are distinguishable from, and are not taught or suggested by Niedzinski et al, Gebeyehu et al., Keener et al., or Kitadai et al. alone or in combination, they are not equivalents. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. MPEP 2144.06; *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). One of ordinary skill in the art would not consider the prior art reference combination since Niedzinski et al teaches away from the use of non-C(3)-functionalized cholesterol derivatives; Gebeyehu involves a limited set of hydrophobic groups and unique linker chemistry, and; Kitadai requires prior transfection of cells *in vitro* by LIPOFECTIN prior to delivery to a subject. As such, no equivalence between hydrophobic groups is taught or suggested, and the prime facie case of obvious is respectfully submitted to have been rebutted.

In light of the above remarks, applicants respectfully request that the rejection of claims 11, 12, 15, and 16 under 35 U.S.C. § 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US

Patent 6,075,012), in further view of Kitadai et al (Br J Cancer 81(14): 647-653, 1999) be withdrawn.

## SUMMARY

Claims 8-16, 19, 20, 22, 24, 26, 27, and 30 are currently pending in this application. Applicant submits that claims 8-16, 19, 20, 22, 24, 26, 27, and 30 are now in allowable form and directed to patentable subject matter. Reconsideration and allowance of the pending claims is solicited. Should the Examiner have any suggestions as to how to improve the form of the pending claims, he is respectfully requested to contact the undersigned attorney in charge of this application.

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Respectfully submitted,

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